

Obesity and Insulin Resistance from Intrauterine Growth Restriction

Intrauterine growth restriction is associated with subsequent risk of **central obesity** and **insulin resistance** in offspring, independent of subsequent body mass index.

General Information	
Broad Focus Area	Obesity and altered physical development
Background and Justification	Birth weight has been inversely associated fairly consistently with increased body mass index later in life, although whether this association is causal remains controversial. ¹ The relation of birth weight to central obesity, conditional on body mass index, however, has been investigated in only a few small studies; ^{2,3} these studies support an inverse association. Although birth weight does not make an important contribution to the population attributable risk of cardiovascular disease, ⁴ this contribution may have been underestimated because birth weight is a poor proxy for the intrauterine events that are related to subsequent risk of obesity, central obesity, and cardiovascular disease. An improved assessment of these intrauterine events can be provided by serial ultrasound examinations during pregnancy. ⁵
Prevalence/ Incidence	<p>IUGR was defined as a birth weight less than the 10th percentile for the gestational age. The prevalence of IUGR was 8.9% and 8.6% for the US Collaborative Prenatal Project (CPP) adulthood survey and the National Health and Nutrition Examination Survey, 1988-1994 (NHANES III), respectively.⁶ About one third of all infants weighing less than 2500 grams at birth have IUGR and approximately 4-8% of all infants born in developed countries and 6-30% in developing countries are classified as growth restricted.^{7,8}</p> <p>The prevalence of overweight among children is greater than 16% among children aged 6 years or more, and this prevalence has increased over the past 40 years.^{9,10} Being overweight as a child is a risk factor for being overweight in adulthood,¹¹ and is associated with increased risk of type 2 diabetes, hypertension, and coronary artery disease.¹² Furthermore, being overweight as a child increases the risk of developing type 2 diabetes before the age of 21 years.¹³</p>
Economic Impact	Because child overweight is a risk factor for adult overweight, child overweight contributes to the more than \$40 billion annual cost of obesity in the U.S. ¹⁴

Exposure Measures		Outcome Measures	
Primary/ Maternal	Fetal size measures (e.g., long bones, head and organ sizes)	Primary/ Maternal	
Methods	Fetal ultrasound	Methods	
Life Stage	Prenatal - 2 nd and 3 rd trimester	Life Stage	
Primary/Child		Primary/Child	<u>Insulin resistance:</u> - Serum insulin levels, Glucose levels, HgbA1C <u>Obesity:</u> - IGF - Body size and habitus - Body composition

Methods		Methods	Blood sample, Physical exam anthropometry, body composition
Life Stage		Life Stage	Birth & periodic

Important Confounders/Covariates	
Lipid profile	Increased lipid levels are associated with an increased risk of insulin resistance ¹⁵
Glucokinase mutation	Glucokinase mutation is associated with increased risk of maturity onset diabetes of the young (MODY) ¹⁶
Hormone levels such as cortisol, growth hormone, insulin-like growth factors	Elevated levels of these and other hormones are associated with obesity and insulin resistance in children ¹⁷
Genetic markers for obesity	Certain genetic markers increase risk of obesity
Parents' body mass indices	BMI and obesity are associated with certain genetic markers. ¹⁸
Family history of diabetes and obesity	A family history of diabetes and obesity increases child's risk. ^{19, 18}
Lifestyle factors	Less active lifestyles would increase risk of obesity and insulin resistance. ¹³
Nutrition	Poor nutritional and high caloric diet would increase risk of obesity and insulin resistance ²⁰
Socio-economic status and demographics	Children of lower economic status, ethnic and racial groups (particularly Native Americans, Hispanics, African Americans, and Asians) are at higher risk of obesity and insulin resistance. ¹⁹

Population of Interest	Estimated Effect that is Detectable
All pregnant women and their offspring.	Using the assumed prevalence of metabolic syndrome as a starting point (0.4%) and estimating that approximately 10% of the study population will have sub-optimal fetal growth, the smallest detectable relative risk in a population of 100,000 is 1.5.

Other Design Issues	
Ethical/Burden Considerations	Blood studies, especially fasting, in younger children will require careful attention. Obtaining consent for the use of DNA may be an issue.
Cost/Complexity of Data Collection	Addressing this hypothesis based on central obesity and insulin resistance measures at later life-stages may be adversely impacted by attrition of study subjects.
Cost of Sample Analysis	While one ultrasound may be included as part of routine prenatal care, additional ultrasounds may introduce added cost.

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